Initiatives for Addressing Environmental Antimicrobial Resistance: Executive Summary

This executive summary highlights key themes from a scientific white paper and discussion at the International Environmental Antimicrobial Resistance (AMR) Forum, a meeting hosted by the U.S. Centers for Disease Control and Prevention, the U.K. Science and Innovation Network, and the Wellcome Trust in April 2018.

This meeting gathered international technical experts, government officials, and other key stakeholders to outline the current knowledge of how resistant microbes and antimicrobials from multiple sources—human and animal waste, antimicrobial manufacturing, and the use of antimicrobials as pesticides—contribute to the presence of resistant microbes and antimicrobials in the environment, the potential impact of the affected environment on human health, and potential next steps to address the risks posed.

This executive summary is supported by the scientific white paper, *Initiatives for Addressing Environmental Antimicrobial Resistance: Current Situation and Challenges*, which was drafted by experts in this field and published alongside this executive summary in 2018, available online at [URL, tbd].

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Graphics in this report were selected from illustrated minutes produced at the International Environmental AMR Forum by Sam Bradd, Drawing Change.

Key Points

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Introduction

Antimicrobial resistance (AMR)—when microbes (germs) develop the ability to defeat the drugs designed to combat them—is a threat to public health and a priority across the globe. To date, AMR scientific research and actions by governments, civil society, and other stakeholders have prioritized focus on antimicrobial use (i.e., antibiotics, antifungals) and preventing spread of AMR in humans and animals. Recently, the focus has expanded to include the role of the natural environment, including in waterways and soils, collectively referenced as "environmental AMR". However, global activity on this topic is still limited.

Scientific evidence shows that antimicrobials and pathogenic AMR—microbes that can cause infections in humans that are difficult or impossible to treat—can be present in the environment and AMR can spread in the environment. For example, bodies of water can act as reservoirs, a place where microbes can adapt, grow, and multiply without hindrance, creating an environment in which resistant strains can thrive. People exposed to antimicrobial-resistant pathogens like Methicillin-resistant *Staphylococcus aureus* (MRSA) in environmental waters are at increased risk of infection from this exposure, including drug-resistant infections that are difficult to treat.

Antimicrobial use can lead to AMR
Antimicrobials are vital tools for health, but their use can lead to an increase in AMR. AMR evolves through a process called natural selection, where organisms better adapted to their environment tend to survive and produce more offspring.

Antimicrobials apply selective pressure to microbes. This is because while some microbes will be killed by the antimicrobial, others resist the effects of the drugs and survive. The resistant microbes that survive pass their resistance trait to their offspring and other microbes, creating more resistant microbes.

The more microbes are exposed to antimicrobials, the more likely it is that resistance traits are passed on and shared.

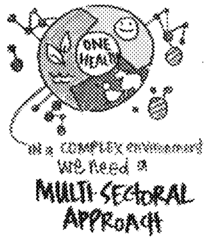
The full extent to which pathogenic AMR and antimicrobials are found in the environment as a result of human activity is not fully understood. However, it is known that antimicrobials and AMR can enter and contaminate the environment in several ways, including from:

- **Human and animal waste (i.e. feces):** Waste from people and animals can carry unmetabolized traces of previously-consumed antimicrobials, including those that are clinically important in human medicine. Waste can also carry antimicrobial-resistant microbes and microbes with resistance genes that can be shared among other microbes.
- **Pharmaceutical manufacturing waste:** Release of active pharmaceutical ingredients (APIs) into the environment can occur when antimicrobials are manufactured.
- **Antimicrobial pesticides for crops:** Some medically important antimicrobials are used on crops to prevent or treat plant diseases. The type and amount of antimicrobials used on crops varies by country.

When antimicrobials or resistant microbes are introduced into the environment, there is an opportunity for these elements to interact with other microbes, including those naturally occurring in these settings. This can accelerate the development and spread of AMR through both the selective pressure applied by antimicrobials, and transmission (spread) of resistance genes between microbes.

There are a number of outstanding scientific questions as to how resistance develops and spreads in the environment and the specific risks environmental AMR poses to human health. More research is needed to address these knowledge gaps, and evaluate the potential risk antimicrobials and resistant microbes in the environment pose to human health and the broader environmental ecosystem.

Despite these ongoing questions, modern trade and travel mean AMR can move easily across borders, with some types of AMR already widespread. Comprehensively addressing AMR requires a collaborative global approach using the One Health framework, which recognizes that the health of people is connected to the health of animals and the environment. A significant number of nations have national action plans (NAPs) to address AMR; however, planned activity to mitigate environmental risks is still limited on a global level. Moving forward, it is necessary to better understand and prioritize environmental risks, and take action to address AMR in the environment where potential risks to human health are greatest. As part of this, it will be important to take into account different AMR sources, transmission pathways, and risks to appropriately prioritize work and resources, and design effective interventions.



Human and Animal Waste

Human Waste

Waste and wastewater can contribute to the development and spread of AMR in the environment, with the potential to negatively affect human health. Antimicrobial residue and microbes, including resistant microbes, exit the human body through waste (feces, urine). Human waste and wastewater (used water from fixtures, like toilets) carrying antimicrobials and resistant microbes are often discharged to bodies of water or land, or, in some cases, wastewater is reused. Studies have found detectable levels of resistant bacteria in surface waters (rivers, coastal waters) as a result of waste contamination, with some people who were exposed to these microbes through interaction with contaminated water becoming ill.

Many countries face challenges in providing adequate sanitation—the ability to dispose of human waste safely and maintain hygienic conditions. In fact, globally, the majority of human waste is discharged directly into the environment without treatment. This includes open defecation and discarding untreated waste into waterways. Access to safe water, adequate sanitation, and proper hygiene education can mitigate environmental AMR and reduce illness and death from common illnesses like diarrhea and infections caused by resistant microbes.

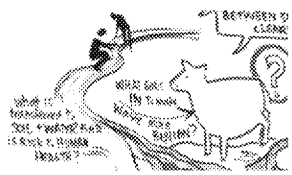
A major component of adequate sanitation is the use of wastewater treatment plants (WWTPs), which reduce contaminants, such as microbes, in wastewater before discharge. However, WWTPs can fail to remove the necessary contaminants before they are discharged into the environment, particularly when the WWTPs are not maintained, have too much water volume (for example, during a storm), or are based on out-of-date technology. In addition, there are questions as to whether traditional WWTPs can sufficiently remove antimicrobials or AMR, particularly when levels of antimicrobial or microbe contamination in the waste are high.

AMR presence in human waste is especially concerning when looking at treatment of wastewater from healthcare facilities like hospitals. Human waste from healthcare facilities is a key source of antimicrobials, harmful microbes, and AMR because patients at these facilities have some of the most resistant infections and are commonly prescribed antimicrobials. The combination of antimicrobials and AMR in hospital waste streams allows resistant microbes to grow in facility plumbing systems, such as sinks, and even inside WWTPs. Healthcare facilities dispose and treat wastewater differently, often dependent on the type, capacity, and location of the facility. Globally, this means that high levels of antimicrobial and pathogenic-AMR might not always be treated sufficiently to avoid environmental contamination. A better understanding of hospital waste treatment in different global settings is a priority. Establishing evidence-based waste standards and developing waste management practices and capabilities would help address this need.

More research is needed to better understand and mitigate the development of AMR from human waste. This includes wastewater assessments for AMR to identify potential contamination and to evaluate WWTP effectiveness, especially when waste is delivered from high volume locations. In some countries, there is also a need for development of wastewater treatment infrastructure and greater use of innovative wastewater treatment technologies that address AMR. Additionally, integrating existing public health initiatives, such as the Water, Sanitation and Hygiene Initiative, will help in the effort to reduce environmental contamination and limit spread of AMR, though this must be done in partnership with the local community.

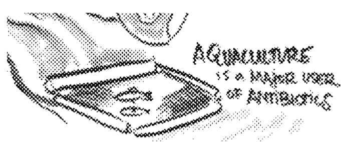
Animal Waste & Aquaculture

Using manure containing antimicrobials or resistant microbes as fertilizer could contribute to the development and spread of AMR through the environment. Animal waste is used as fertilizer on agricultural lands to help stimulate plant growth and maintain productive soils. However, similar to human waste, manure from food-producing animals that have been treated with antimicrobials can carry antimicrobial residue and resistant microbes, which could potentially contaminate the surrounding soil and nearby water sources. Further research is needed to fully determine the effects of animal waste contamination on human health and the broader environmental ecosystem, though there are known cases of people becoming ill from an AMR pathogen through contact with food animals or their manure.



Manure is often processed prior to use as fertilizer, but the level of treatment is dependent on setting, and further research is still needed to understand how effective different treatments are at reducing antimicrobials and resistant microbes before application. Resistant microbes can also be introduced via biosolids—fertilizer material composed of treated human waste—but again, it is unclear how effective removal strategies are at eliminating contaminants. Research is also needed to better understand the impact of trace contaminants in manure and biosolids entering the environment. However, recent studies suggest human exposure and environmental transmission does occur, particularly in settings where communities live closer to livestock. Manure-treatment standards and evaluation of treatment options for reducing AMR could be viable options for reducing risk to humans.

Antimicrobials are also used worldwide in aquaculture, the farming of fish and seafood, to control disease. Aquaculture supplies more than half of all global seafood, and using antimicrobials in these settings could lead to AMR that affects human health, though the direct risk continues to be unclear.



In aquaculture, antimicrobials are generally administered in feed or occasionally through bath treatments, potentially contaminating the local aquatic environment with antimicrobial residue through fish waste matter and discharge of dissolved antimicrobials into the water column. This form of antimicrobial use, if not practiced sustainably, could drive resistance development. Data on antimicrobial use is limited, such as estimates of total sales and exact use of antimicrobials for aquaculture, which impacts comprehensive risk assessments.

Contamination of the environment with animal and fish waste containing antimicrobial residue could be reduced through appropriate use of antimicrobials in animal agriculture and aquaculture. The development of alternative disease control methods, such as vaccination-based strategies, could reduce reliance on use of antimicrobials without diminishing yield or quality of livestock produced. In addition, establishing better early warning systems for the emergence of disease and improving the quality of the rearing environment can help reduce the need for antimicrobials. These actions will help reduce the level of antimicrobial residue in waste to limit environmental contamination, and also support goals to improve stewardship of antimicrobials in animals. However, in some cases, work is needed to develop these methods and support their implementation in such a way that both animal welfare and business sustainability is maintained.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action. Unless specified, these apply to both human and animal waste:

Assessing Environmental Waters

- Assess where and how much resistant microbes are present in environmental waters to better understand the risk of AMR to human health
- Conduct studies to understand the drivers of AMR in recreational and drinking water, including identifying sources of resistant pathogens (human or animal) and selective pressures driving amplification and transmission of AMR in these waters
- Evaluate sampling strategies and testing methods to measure AMR in environmental waters to identify best practices

Assessing and Improving Sanitation & Wastewater Treatment

- Evaluate the need for on-site pretreatment of wastewater for facilities that may contribute AMR in the environment (e.g., hospitals) by conducting studies of the environment near waste discharge and assessing the impact of approaches to limit AMR and antimicrobial discharge
- Conduct studies to evaluate the effectiveness of existing wastewater treatment processing for removal of antimicrobial-resistant microbes and antimicrobials from wastewater before discharge into environmental waters. Investigate and identify factors that result in treatment inefficiencies and failures (e.g., ineffective processing methods or infrastructure failures)
- Improve sanitation globally by conducting research to identify efficient and affordable wastewater processing methods that are easily implemented where processing doesn't currently exist or as enhancements to existing processing where levels of AMR are high

Assessing Environmental AMR from Agriculture

- Conduct research to identify and develop alternatives to antimicrobials to prevent and control disease on the farm and in aquaculture
- Evaluate methods for treating animal manure and human waste biosolids when using these as fertilizers on the farm to prevent environmental contamination with AMR and antimicrobials

Manufacturing Waste

The manufacturing of antimicrobials by pharmaceutical companies can contribute to the development of environmental AMR. In some cases, manufacturing process effluent (waste discharged into a body of water) can include antimicrobials, resistant microbes, and active pharmaceutical ingredients (APIs)—even after treatment—and might be discharged directly into the local environment. For example, studies have found APIs in rivers, treated or untreated manufacturing wastewater, and sediment downstream of industrial wastewater treatment plants. The levels of antimicrobials and APIs found in the environment can be very high, with evidence to show that release of effluent can bring about an increase in levels of resistance in the local waters. The full extent to which AMR linked to manufacturing waste directly affects human health is not fully understood; however, this waste is an important and often neglected source of antimicrobials and of AMR contamination in the environment, specifically in countries where antimicrobials are manufactured.

Eliminating or significantly reducing antimicrobial residue and other contaminants in manufacturing waste is a critical step in mitigating environmental AMR. However, at this time, there are no globally agreed upon and enforced standards to limit the level of contamination in manufacturing effluent because a "safe discharge limit" has not been established. In an effort to minimize impact of antimicrobials discharged from manufacturing processes, some companies have set voluntary effluent limits as part of their own environmental risk-management strategies.

Data on the amount of APIs released in wastewater discharges is not publicly available, making it difficult to understand the full scope of the problem and determine an optimum risk management approach. At the same time, while methods to analyze APIs in discharged manufacturing wastes and in aquatic environments exist, an internationally recognized standard method is needed to feed into risk assessment and compare results from different factories.

Addressing these data and methodology gaps would help researchers identify risk to human health and guide viable and effective actions to mitigate this risk. As a priority, fostering agreement on a discharge limit for effluents leaving manufacturing sites (i.e., not zero, but sufficiently low to be protective while still being technically achievable) and reporting effluent levels could significantly reduce environmental contamination. A subset of the industry has already provided leadership on best practices for responsible waste management, with several voluntary industry initiatives for responsible manufacturing and sourcing already underway. More action and collaboration across industry, academia, and governments is still needed to better understand and manage manufacturing waste.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action:

- Develop and validate standardized monitoring methods for testing antimicrobial agent runoff from the manufacturing process
- Conduct pilot studies to evaluate the feasibility and cost of limiting discharge to discharge targets (i.e., discharge limits) proposed by scientific experts
- Identify and evaluate incentives (e.g., green procurement) to reduce pharmaceutical manufacturing contaminants in a timely and effective way
- Identify or develop strategies to limit environmental contamination in countries where antimicrobial manufacturing occurs. Work with industry partners, such as the AMR Industry Alliance, to evaluate and implement strategies

Antimicrobial Pesticides for Crops

Antimicrobials are commonly applied across the globe as pesticides to manage crop disease. These diseases can be difficult to control and extremely damaging, impacting the income of farms and the local and global food supply if left untreated. However, applying antimicrobials might accelerate the development and spread of AMR in the environment by contaminating the surrounding soil and water during application or subsequent run-off from farmland. While further research is needed to determine the effects of antimicrobial-based pesticides on human health and the broader environmental ecosystem, there are specific concerns for human health where antimicrobial pesticides are the same as, or closely related to, antimicrobials used in human medicine.

There is evidence of microbes developing resistance to antimicrobial pesticides, and, in some cases, these microbes also cause human infections. For example, triazole is the most widely used fungicide on crops, but is also important in human medicine to prevent or treat fungal infections. Already some human triazole medications are no longer effective following the development of resistant fungi such as *Aspergillus fumigatus*. Additionally, while copper formulations are not used in human medicine, their use as a pesticide may contribute to resistance to antimicrobials used in human medicine through co-selection pressure. There is also an increased risk to human health through the exposure of workers who apply antimicrobial pesticides. In some countries, pesticide applicators wear personal protective equipment, but there is limited knowledge on how effective the equipment is at minimizing exposure to the antimicrobial pesticide.

In terms of surveillance, comprehensive information is not collected on which antimicrobials are being used, where, and at what levels. Collecting, monitoring, and analyzing this data would greatly support the identification of possible links between antimicrobial pesticides and the emergence of resistant microbes that cause human infections. This data would also guide research to determine the impact of antimicrobial pesticides on the surrounding environment, including soil, water, plants, and animals. Additionally, principles grounded in scientific evidence in national AMR action plans around antimicrobial pesticide use could be considered. Support is needed to identify and develop alternative disease prevention and treatment strategies, such as integrated pest management or modeling to predict high-risk periods for crop disease. These actions could help improve antimicrobial use and minimize exposure to humans and the surrounding environment, which would mitigate the potential risk to human health.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action:

- Conduct research to determine the potential impact of antimicrobial pesticide exposure on the human, plant, and animal microbiomes after pesticide application
- Identify and promote best management practices when applying antimicrobials as pesticides to minimize exposure to humans, animals, and the surrounding environment
- Establish greater global transparency of antimicrobial use as pesticides by collecting and sharing information like the amount of antimicrobials used on crops each year
- Share data between countries on the relative efficacy of antimicrobials as pesticides and potential alternatives, so that antimicrobials used in human medicine are only considered when there is evidence of efficacy and no alternatives are available
- Conduct studies to develop efficacious and feasible alternatives to antimicrobials to prevent or treat crop disease and identify strategies to ensure that alternative treatments are available to growers
- Identify and develop appropriate and reproducible methods to monitor the crop field and surrounding environment to determine if there are increases in antimicrobial resistance when medically important antimicrobials are used and when co-selection is a concern
- Consider updating national AMR action plans to include antimicrobial stewardship principles for using antimicrobials as pesticides with actions that are based upon country-specific practices

Conclusion

Environmental contamination by antimicrobials and resistant microbes presents a significant challenge to the global community in the effort to combat AMR. Scientific evidence shows that antimicrobials and pathogenic AMR are present in the environment, AMR spreads in the environment, and this form of environmental contamination may affect human health. Effective action is reliant on more scientific, risk-based data to address the gaps and fully understand the potential risks posed by antimicrobials and resistant microbes in the environment. Specifically, greater clarity is needed on the risk to human health in order to prioritize action on environmental AMR.

The scientific, risk-based data should be built from standardized indicators, methods, and targets that measure and monitor antimicrobial contamination and resistance in different environmental settings. Conducting local AMR assessments of the environment and sharing data across countries and sectors can help to provide a more comprehensive understanding on AMR in the environment, and, where possible, AMR assessment data should be integrated with data from public health surveillance programs.

As a key pillar of the One Health framework, the environment should be elevated on the global AMR agenda and better integrated into wider AMR mitigation activities. Despite knowledge gaps, there is a need to better translate the evidence we do have into clear priorities that will support greater progress in the field of environmental AMR. For example, there are a number of high-risk areas, such as disposal of waste from healthcare facilities and manufacturing, which could be prioritized and addressed on local and global levels to reduce potential risks to human health posed by environmental AMR. In fact, there has been recognition by industry to establish recognizable discharge limits for effluent leaving manufacturing sites to address contamination and risk of environmental AMR.

The threat of AMR in the environment is a global issue that varies greatly from country to country. As a shared global challenge, it will be important to have a globally led approach to environmental AMR with locally relevant interventions. Moving forward, stakeholders can work to understand their local situation, determine what action is both beneficial and feasible, and move towards reducing identified risks to public health. This local action can be combined with already-existing global public health collaborative efforts, such as the Sustainable Development Goals; the Water, Sanitation and Hygiene Initiative; and the Global Health Security Agenda. These efforts can also be strengthened by integrating environmental AMR activities.

As we improve local, national, and international understanding of AMR in the environment, and as we work collaboratively to enhance collective scientific understanding, we will be able to better identify best practices, recommendations, and actions that are most significant and can be considered for wider adoption.

This executive summary and the supporting white paper, developed in partnership with the assembled technical experts that participated in the International Environmental AMR Forum in 2018, highlight data identifying the potential for the environment to be a source of AMR pathogens that can affect human health. They also highlight the significant knowledge gaps and measures that could be most important for mitigating risks. This information is intended to act as a roadmap for stakeholders, including researchers, non-governmental organizations, and countries, to work in collaboration to fill knowledge gaps and improve national and international understanding on how to best evaluate and address AMR in the environment.